## *Remarks*

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-14, 22-40, 47-88, and 90-92 are pending in the application, with 1, 47, 48, 51, 57, 64, 66, 73, 76, and 83 being the independent claims. Support for the amendments are found in the claims as originally filed. Claims 89, 93, and 97 are sought to be canceled without prejudice to or disclaimer of the subject matter therein. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

***Election/Restriction***

Claim 49 has been rejected as being drawn to an improper Markush grouping. The Examiner is of the opinion that claim 49 has not been amended with respect to $A^2$ in terms of $A^2$ being a monocyclic ring containing a total of 7 ring atoms. (Office Action, page 2).

Applicants respectfully disagree. Claim 49 as amended refers only to compounds wherein $A^2$ is a monocyclic ring selected from heteroarylene or unsaturated, partially unsaturated, or saturated heterocycloalkylene containing a total of 7 ring atoms. Therefore,

Applicants respectfully submit that the Examiner's stated grounds for rejection have been accommodated and the rejection should be withdrawn.

***Rejections under 35 U.S.C. § 112***

***A. First Rejection (Claims 1-14, 22-40, 47-93 and 97)***

Claims 1-14, 22-40, 47-93 and 97 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to enable one skilled in the art to use the invention. (Office Action, pages 2-3). Applicants respectfully traverse this rejection.

Claims 89, 93, and 97 have been canceled rendering this aspect of the rejection moot.

In the interest of advancing prosecution and without acquiescing to the rejection, claims 1-14, 22-25, 27-40, 47-54, 57, 60-74, and 76-84 have been modified to delete any reference to prodrugs. Therefore, Applicants respectfully submit that the Examiner's stated grounds for rejection have been accommodated and the rejection should be withdrawn.

***B. Second Rejection (Claims 54-88 and 97)***

Claims 54-88 and 97 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. (Office Action, pages 4-14). Applicants respectfully traverse this rejection.

Claims 89, 93, and 97 have been canceled rendering this aspect of the rejection moot.

The Examiner points out that there are over 200 cancerous conditions, listing them all. The Examiner then cites case law from M.P.E.P., 2164.08 without applying it to the facts at hand. Applicants respectfully disagree with the Examiner's conclusion.

The Examiner has failed to provide any reasoning or argument for maintaining the present rejection. Merely listing every known type of cancer is not sufficient to establish a lack of enablement for the present claims. While the claims may encompass the treatment of numerous types of cancer, the specification provide sufficient enablement for the full scope of the claims. Applicants provided detailed evidence supporting the enablement of the claims in the response filed July 23, 2003. The Examiner has failed to address any of these arguments. The arguments are therefore repeated below.

In order for the present claims to be enabled for the treatment of cancer, it is sufficient that the class of compounds as a whole described in the claims has caspase activating activity and that administration of compounds having such activity is capable of treating cancers in general. To the extent that any particular compound within the genus is not effective or that any particular type of cancer does not respond to the administration, these are merely inoperative embodiments of the claimed invention. As long as the skilled artisan can readily determine which embodiments are inoperative without undue experimentation, the invention as a whole is enabled. See M.P.E.P. 2164.08(b). The examples disclosed in the present specification involving three types of cancer cells and five different compounds of the claimed invention indicate that the compounds are effective in inducing apoptosis in cancer cells. The Examiner has provided no specific evidence to show that this activity is not common to all the compounds encompassed by the invention, that the

disclosed examples are not predictive of effective treatment of cancer *in vivo*, or that any cancer would not be sensitive to the induction of apoptosis. The enablement of the present claims does not depend on the identification of a single compound capable of curing all cancers. The assays disclosed in the specification are predictive of *in vivo* efficacy and the Examiner has failed to provide any evidence to the contrary. In the absence of any such specific evidence showing that the specification is not enabling for the claimed invention, the invention must be considered to be enabled.

Additionally, Applicants provided evidence of the broad applicability of the present invention in the response filed February 5, 2003. The Examiner has failed to address this evidence. It is now known that cancer cells are, *inter alia*, generally characterized not only by a loss of cell cycle control but also by resistance to apoptosis. *See generally* Raymond W. Ruddon, *Biochemistry of Cancer, in* Holland-Frei Cancer Medicine, Chapter 2 (Robert C. Blast, Jr., *et al.* eds., 5th ed., B.C. Decker, 2000), a copy of which was submitted as Document AT19 in the First Supplemental Information Disclosure Statement filed February 5, 2003. Consequently, increasing the rate of apoptosis is recognized by those of skill in the art as an effective method for the treatment of a wide variety of cancers. *See, e.g.*, WO 00/04901, page 3, line 3, through page 5, line 6, a copy of which was submitted as Document AL2 in the First Supplemental Information Disclosure Statement filed February 5, 2003. Indeed, caspase activation is recognized, by those of skill in the art of cancer therapy, as a crucial requirement for the sensitivity of tumor cells toward drug-induced cell death. *See, e.g.*, Maret Los, *et al.*, "Cross-Resistance of CD95- and Drug-Induced Apoptosis as a Consequence of Deficient Activation of Caspases (ICE/Ced-3 Proteases)," *Blood 90*:3118-3129, 3128 (1997), a copy of which was submitted as Document AT9 in the

Information Disclosure Statement filed November 4, 2002. Therefore, it is now recognized by those of skill in the art that agents that increase the rate of apoptosis are effective for the treatment of a wide variety of cancers.

For the reasons stated above, Applicants respectfully submit that the evidence submitted herewith is effective to rebut a *prima facie* case for non-enablement of claims 54-88 and 97, under 35 U.S.C. § 112, first paragraph, and that the rejection should be withdrawn.

### *C. Third Rejection (Claims 57-65, 89-93, and 97)*

Claims 57-65, 89-93, and 97 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. (Office Action, pages 14-15). Applicants respectfully traverse this rejection.

Claims 89, 93, and 97 have been canceled rendering this aspect of the rejection moot.

The Examiner is of the opinion that:

> [t]he applicants' stated that "it is well known to those of skill in the art what disorders are responsive to the induction of apoptosis" and O'Reilly and Orrenius are cited in support. O'Reilly is speculative at best with respect to the induction of apoptosis as a mode of treatment for autoimmune disease.
>
> The scope of the method claims are not adequately enabled for the treatment of the asserted diseases and/or disorders in the specification, nor is there any testing to indicate that the compounds of the instant invention are effective in the treatment of the asserted diseases ad/or disorders.

(Office action, pages 14-15).

Applicants respectfully disagree. The Examiner has failed to make a *prima facie* case for lack of enablement as she has provided no reasoning to support the conclusion that the claims are not adequately enabled. A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). Examples of particular diseases and its symptoms the invention is used to treat can be found in the specification, *inter alia*, at page 35, line 15, through page 36 line 5. Additional diseases are disclosed in the specification at page 38, line 24 through page 41, line 30. Furthermore, methods of treatment are described, *inter alia*, at page 36, line 6 through page 38, line 9 and at page 42, line 1, through page 46, line 10. Finally, the specification describes the animals intended to be treated with the invention on page 27, lines 13-15. The Examiner has not provided any evidence to show that the truth of these statements should be doubted.

The Examiner further states that no testing has been done to prove the effectiveness of the treatment. However, there is no requirement for working examples in order for a claim to be enabled. See M.P.E.P. 2164.02.

Therefore, Applicants respectfully submit the Examiner has not established a *prima facie* case of non-enablement of claims 57-65, 89-93, and 97 under 35 U.S.C. § 112, first paragraph; and Applicants respectfully request that the rejection be withdrawn.

***D. Fourth Rejection (Claims 1-14, 22-40, 47-93, and 97)***

Claims 1-14, 22-40, 47-93, and 97 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, pages 15-16). Applicants respectfully traverse this rejection.

Claims 89, 93, and 97 have been canceled rendering this aspect of the rejection moot.

In the interest of advancing prosecution and without acquiescing to the rejection, claims 1-14, 22-25, 27-40, 47-54, 57, 60-74, and 76-84 have been modified to delete any reference to *N*-oxide derivatives and protected derivatives.

The Examiner is of the opinion that the claims are indefinite in that:

> [t]he scope of disease and/or disorders associated with the induction of apoptosis such as autoimmune diseases is speculative at best as pointed out in the response to the scope of enablement cited above. It is not known at this time whether all of the diseases and/or disorders urged by the applicant are treatable by the induction of apoptosis.

(Office Action, page 16).

Applicants respectfully disagree. As discussed above, a long list of diseases and their symptoms the invention may be used to treat can be found in the specification, *inter alia*, at page 35, line 15, through page 36 line 5. Additional diseases are disclosed in the specification at page 38, line 24 through page 41, line 30. Thus, the specification adequately discloses diseases and disorders that are responsive to the induction of apoptosis. However, in the interest of advancing prosecution and without acquiescing to the rejection, claims 57 and 64 have been amended to recite a specific list of disorders responsive to the induction of apoptosis. The metes and bounds of the claims are therefore clear and definite. The

specification indicates that each of the listed disorders is responsive to the induction of apoptosis. The Examiner has not provided any evidence to the contrary.

Applicants respectfully submit that the Examiner's stated grounds for rejection have been accommodated and the rejection should be withdrawn.

### *E. Fifth Rejection (Claim 97)*

Claim 97 has been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession if the claimed invention. (Office Action, pages 16-17). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that "rheumatoid arthritis and lymphoproliferative syndrome are not described in the specification as autoimmune diseases." (Office Action, page 16).

Applicants respectfully disagree. Claim 97 has been canceled, rendering the rejection moot. Therefore, Applicants respectfully submit that the Examiner's stated grounds for rejection have been rendered moot and the rejection should be withdrawn.

### *F. Sixth Rejection (Claims 12, 34, 53, 60, 62, 69, 71, and 81)*

Claims 12, 34, 53, 60, 62, 69, 71, and 81 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, pages 17-18). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that claims 12, 34, 62, 71, and 81 "recite the limitation "2-....-3-hydroxy-cyclohex-2-enone" in the species on pages 14, 20, 39, 54, 55 and 70, respectively. There is insufficient antecedent basis for this limitation in the claim." (Office Action, page 17).

Applicants respectfully disagree. Claims 12, 34, 62, 71, and 81 each refer to compounds in which $A^1$ is a 2-hydroxy-6-oxo-cyclohex-1-enyl group. Support for this group is found in parent claims 11, 33, 60, 69, and 79, respectively. When naming the compounds in claims 12, 34, 62, 71, and 81, however, the nomenclature convention is to refer to the same $A^1$ group as a 2-substituted-3-hydroxy-cyclohex-2-enone. Thus, the claims have proper antecedent basis.

The Examiner is of the opinion that claim 53 is indefinite as there is insufficient antecedent basis for the limitation $-R^{9'}$ in the claim. "It is believed that the applicants' intended $X^2R^{9'}$." (Office Action, page 18).

Applicants respectfully disagree. Claim 53 as amended recites in part "$A^3$ may be substituted with a group selected from $X^2R^{9'}$." Thus, the claim is not indefinite.

The Examiner is of the opinion that claims 60 and 69 are "vague and indefinite in that it is not known what is meant by the definition of $A^2$ which is as defined above. However, $A^2$ is not defined within the claim." (Office Action, page 18).

Applicants respectfully disagree. Claims 60 and 69 as amended indicate that $A^2$ is as defined in Claims 57 and 66, respectively. Thus, the claims are not indefinite.

Applicants respectfully submit that all of the stated grounds for the rejection of claims 12, 34, 53, 60, 62, 69, 71, and 81 under 35 U.S.C. § 112, second paragraph, have

been traversed, accommodated or rendered moot. Therefore, Applicants respectfully submit that this rejection should be withdrawn.

***Correction of Inventorship***

On July 24, 2003, Applicants filed, *inter alia*, a Request to Correct Inventorship to add Martin Sendzik to the inventive entity. Applicants respectfully request that the Examiner grant this Request and indicate in the file history that Martin Sendzik has been added to the inventive entity.

## *Conclusion*

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Robert A. Schwartzman, Ph.D.
Agent for Applicants
Registration No. 50,211

Date: October 29, 2003

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600